Measuring symptomatic relief in men with lower urinary tract symptoms

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EDITORIALS

Measuring symptomatic relief in men with lower urinary tract symptoms

Most currently used drugs have been given too easy a ride

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Lower urinary tract symptoms are common in the ageing population and have many causes.[1] In men the various symptoms are still often attributed to benign prostatic hyperplasia, whatever their true cause[2] and despite the remarks repeatedly made about nomenclature.[3] Recently published guidelines and reviews on the evaluation and treatment of men with lower urinary tract symptoms rate four categories of drugs as efficacious: α blockers, 5-α reductase inhibitors, anticholinergics, and phosphodiesterase-5 inhibitors. [1 2 4 5]

We are surprised at how highly these drugs are recommended given how well they work. While treatment effects are reported as being significantly better than those of placebo, we wonder whether the small differences in patient-reported symptom scores are perceptible to patients.

Most drugs used for these symptoms were investigated using the International Prostate Symptom Score (IPSS), equivalent to the American Urologic Association (AUA) Symptom Index. This index has seven questions and yields scores ranging from 0 to 35, with higher scores indicating more severe symptoms. About 20 years ago, Barry and colleagues estimated the smallest perceptible change in the AUA symptom index in 1222 men participating in randomised controlled trials investigating treatment for benign prostatic hyperplasia.[6] Patients considered a 3 point fall in symptom score a "slight" improvement (table⇓), and since then a 3 point change in score has been regarded as clinically relevant when assessing treatments. This cut-off has never been challenged.

What matters to patients

From the patient's viewpoint, it seems highly arguable that a slight improvement should be regarded as clinically relevant. Who would willingly take any drug that carries the risk of (more or less) severe side effects and drug interactions,[7] for only a slight improvement in symptoms? In nearly all randomised trials of drugs for lower urinary tract symptoms, changes in different treatment arms are presented as mean scores. In most cases, the differences between active and placebo treatments are reported as "statistically significant," but we doubt this usually reflects a clinically relevant change. We found that a difference of more than 3 points was reported in only four out of 28 studies.[8-33] In these studies the mean decrease in the IPSS score was 6.8 (tamsulosin *v* placebo),[8] 3.1 (doxazosin and finasteride *v* placebo, but in combination not better than doxazosin monotherapy),[9] 3.9 (terazosin *v* placebo),[10] and 3.1 (terazosin and finasteride *v* placebo, but in combination not better than terazosin monotherapy).[11] Therefore, hardly any of the available drugs is better than placebo at a "clinically relevant" level. At best, there is less than a "slight" difference in favour of active treatment.

Because published studies report mean scores, some participants will have had larger improvements. However, from all available data it remains unclear how many participants taking active medication would have experienced moderate or substantial improvement in symptoms. Such information is essential to provide patients with reliable information about treatment.

Another study examined the effects on symptom worsening and complication rates over four years. Even in the high risk patients included in this trial, the complication rate was low. As a consequence, the numbers needed to treat derived from this trial were very high.[12]

There is an urgent need to publish data on the efficacy of drugs prescribed for lower urinary tract symptoms, in particular on the chances of achieving a clinically relevant change. We believe that a "moderate" (5 points) or "marked" (9 points) improvement (as defined by Barry and colleagues) should be used to define clinically relevant change, and meta-analyses of large randomised trials using this cut-off should be performed. We encourage authors and drug companies to make their data available for such analysis. In addition, future studies testing new treatments could use this cut-off in power analyses. This would enable physicians to provide better treatment and advice for the increasing number of men who consult them for lower urinary tract symptoms.

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Table

Table 1| Relation between mean absolute change in American Urologic Association symptom index (range 0 to 35) and patients' 13 week global assessment of change

Mean (SE) change in symptom score*	Patient assessment of improvement
- 8.8 (0.34)	Marked
- 5.1 (0.29)	Moderate
- 3.0 (0.27)	Slight
+ 2.7 (0.93)	Worse

* Change between baseline and follow-up assessment in 1222 men participating in randomised controlled trials (derived from Barry et al[6]).